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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/104,340	06/25/98	BOYD A	FISHR11.001A

HM12/1025

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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	8

DATE MAILED: 10/25/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/104,340	Boyd et al
Examiner	**Group Art Unit**
Nirmal. S. Basi	1646

☒ Responsive to communication(s) filed on *Jul 26, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12, 20-24, and 34-42* is/are pending in the application.

Of the above, claim(s) *21-24 and 42* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12, 20, and 34-41* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-12, 20-24, and 34-42* are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Supplemental Preliminary Amendment filed 7/26/99 has been entered. Preliminary Amendment filed 6/25/98 has been entered.

Election/Restriction

2. Applicant's election of Group I Claims 1-12 and 20; cancellation of claims 13-19 and 25-33; addition of claims 35-43 (renumbered as 34-42), in Paper No. 7 (7/26/99), is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-12, 20 and newly added claims 34-41 directed to the Invention of Group I will be examined in this application. Newly added claim 42 will not be examined because it is directed to a non-elected invention, i.e. the invention of Group II.

Specification

3. This application is informal in the arrangement of the specification. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

The application should have the "Title of the Invention" at the top of the first page followed by "Cross-References to Related Applications" which in turn should be followed by the title "Background of the Invention". It is suggested the names and addresses of the authors be removed following the title. The application should also include the heading "Detailed Description of the Invention".

FIG. 10E, 10F and 3G and FIG. 11 must be must described separately in the Brief Description of the Drawings. The description of the afore mentioned FIGs is missing. Further, FIG.5 should be refered to as FIGS. 5A-C, FIG. 6 as FIGS. 6A-D and FIG. as FIGS 9A-D. The specification does not include page 25.

Appropriate correction is required.

5. ***Sequence Rules Compliance***

This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states "reference must be made to the sequence by use of the assigned identifier", the identifier being SEQ ID NO. Sequence in Figure 1, on page 19 must be identified by its corresponding SEQ ID NO:. Correction is required throughout the specification. Also application fails to comply with the Sequence Rules, 37 CFR 1.821 et seq., because claims 4, 5, 6, 7, 11, 37 refer to an amino acid sequence without reference to a SEQ ID NO: identifier. Compliance with sequence rules is required.

Appropriate correction is required.

Claim Rejection, 35 U.S.C. 112

6. Claims 1-8. 11-12, 20, 34 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4, 5, 11 and 12 are indefinite because it is not clear what comprises a "an Eph family RTK" so as to allow the metes and bounds of the claim to be determined. The claims nor specification disclose what constitutes the "an Eph family RTK" and how such is determined.

Claims 1-4, 20, 34, 37 are indefinite because it is not clear what comprises a "ligand-binding domain" so as to allow the metes and bounds of the claim to be determined. The claims nor specification disclose what constitutes the "ligand-binding domain" of an Eph family RTK. It is suggested "ligand-binding domain" be described by SEQ ID NO:. Further it is suggested that "RTK" be replaced with receptor protein-tyrosine kinase.

Claims 4-7, 11 and 37 are indefinite because it is not clear what amino acid sequence the "ligand-binding domain" is referring to so as to allow the metes and bounds of the claim to be determined.

Claim 11 is indefinite because it is not clear what comprises a "ligand-binding domain" so as to allow the metes and bounds of the claim to be determined. Therefore if it is not clear what comprises a "ligand-binding domain" it is further unclear what comprises a sub-sequence of said domain. Also, if it is not clear what comprises a " ligand-binding domain" it is further unclear what comprises a "homolog of a ligand-binding domain". Further, it is not clear what constitutes a "homolog" so as to allow the metes and bounds of the claim to be determined. The determination of homology is not an absolute, but dependent upon the algorithm being used, and the way in which that algorithm is applied. Parameters which must be specified in determining homology of two sequences include allowance of gaps and gap penalty, and allowance for

substitutions and the penalty for such. Without knowing what algorithm is being used to calculate homology, and what the setting for such parameters are, one cannot determine the metes and bounds of all sequences which would meet the limitation of being 'X% identical' to the recited sequence. There is no reference to any specific mathematical algorithm utilized for the comparison of two sequences and the specification or the claims give no definition of the parameters actually used to calculate homology of the ligand binding domain in instant application. If any one of the algorithms present in the literature were used to determine identity it is not clear as to how gaps are to be assessed in determining identity where gaps are required to optimally align two sequences of unequal length. This ambiguity may be demonstrated by the following examples: consider two sequences, ABCDEF and ABEF. These could be compared in four ways:

ABCDEF	4/6 = 67%	ABCDEF	2/6 = 33%
AB---- EF	4/4 = 100%	ABEF	2/4 = 50%

In the absence of a disclosure of the algorithm by which "homology" is to be determined, the claims can only be considered definite if comparisons are limited to sequences of identical length. To illustrate this issue, see George, et al. (Ref. A).

Claim 8 is rejected for depending upon an indefinite base (or intermediate) claim and it fails to resolve the issues raised above.

35 U.S.C. § 112, first paragraph

5. Claims 1-2, 4-8,10-12, 20 and 34-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence disclosed in SEQ ID NO:4 or encoded by SEQ ID NO:5 (i.e. encoded by exons I-III of HEX), wherein said polypeptide binds LERK7, does not reasonably provide enablement for other polypeptides. The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While the person of ordinary skill in the art would, in light of the specification be able to isolate a polypeptide containing exons I-III of HEX, wherein the polypeptide binds LERK7, the scope of the claims, which encompass other polypeptides without LERK7 binding activity are not enabled by the disclosure. The disclosure does not teach how to use a commensurate number of the polypeptides which do not share the LERK7 binding activity functions. The disclosure teaches the binding of LERK7 to HEK encoded by exons I-III and further discloses that LERK7 does not bind to polypeptide encoded by exons I-II (FIG. 2F). Also disclosed is, "no expression was observed for any of the protein constructs containing the exon III encoded domain, but missing the first 31 amino acids of the mature HEK protein (encoded by exons I and II; amino acids 21-25 of the sequence shown in FIG. 1)", see page 38, line 17 -23. Therefore, the specification discloses the interaction of LERK7 with the domain of the HEX protein encoded by exons I-III but also suggests that said domain is critical for binding of LERK7. The disclosure

fails to teach how to use to use a commensurate number of the polypeptides which do not share the LERK7 binding activity functions.

Further the disclosure fails to teach what are boundaries of the ligand binding domain or what is considered a homolog of the ligand binding domain. Would the polypeptide domain encoded by exons I-III of HEX which bind LERK7 be considered ligand binding domain, would the polypeptide domain encoded by exon III which bind LERK7 be considered ligand binding domain, would the polypeptide domain encoded by exons I-VII which bind LERK7 be considered ligand binding domain, would the specific amino acid residues which bind to LERK7 be considered ligand binding domain etc. Further, what is considered the ligand binding domain in other Eph family RTKs? Also not disclosed are what sub-sequences of a ligand bing domain of an EPH family RTK, or homolog of ligand bing domain of an Eph family RTK, bind LERK7 or other ligands. In particular, pertaining to claims 11 and 12 , due to the large quantity of experimentation necessary to identify the polypeptides containing no disclosed structure and function, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:4 are also encompassed by the claim), and the breadth of the claim which fail to recite structural and functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

6. **Claim Rejections, 35 U.S.C. 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-12, 20, 34-41 rejected under 35 U.S.C. 102(a) as being anticipated by Boyd et al (Ref B, U. S. Patent No. 5,674,691).

Boyd et al teach the polypeptide of SEQ ID NOs: 1-4 encoded the plynucleotide of SEQ ID Nos: 5-8 (see SEQ ID Nos :9 and 10). The sequences disclosed by Boyd et al are for HEK. The receptor-type tyrosine kinase (HEK) is identified as a member of the eph/elk family of tyrosine kinases (column 1, last paragraph). Further disclosed is "ligands for HEK are capable of being screened for in a number of ways. In one protocol, an expression vector (e.g. AP-TAG-HEX) is selected which encodes the entire extracellular region of HEK fused to an appropriate reporter molecule like alkaline phosphatase. The fusion protein expressed in cells is recovered from cell supernatants and used to stain tissue sections"(column 6, last paragraph). Also disclosed is that the fusion protein can be used to assay ligand activity (column 6, first paragraph and last paragraph). Column 11, second paragraph discloses the structural features of HEX which include, signal peptide, transmembrane domain, extracellular domain which is rich in cysteine residues. The extracellular domain of HEK protein (is considered by the examiner to be the ligand binding domain since ligands can bind to this domain) inherently binds to LERK7 absent evidence to the

contrary. The disclosure of Boyd et al meets all the limitations of claims 1-12, 20, 34-41 since the disclosed extracellular domain comprises or has the domains encoded by exons I-III of instant invention.

Art made of record and not relied upon is considered pertinent to applicants disclosure:

Reference C Bennett et al U. S. Patent No. 5,864,020. HTK ligands.

Reference D Bennett et al U. S. Patent No. 5635,177. Protein tyrosine kinase agonist antibodies.

Reference E Zhou et al U. S. Patent No. 55,814,479. BSK receptor-like tyrosine kinase.

Reference F Maisonpierre et al U. S. Patent No. 5,843,7498. EHK and ROR tyrosine kinases.

Reference G Pasquale et al U. S. Patent No. 5,547,048. EPH-related tyrosine kinases nucleotide sequences and methods of use.

Reference H Beckman et al U. S. Patent No. 5,738,844. Cytokines that bind the cell surface receptor HEK.

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Thursday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
October 19, 1999

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Nirmal S. Basi
Art Unit 1646
October 19, 1999

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER